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EXAMINER	
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ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,583	PLESTED ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *19 and 29-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20-28* is/are rejected.

7)☒ Claim(s) *1,9,13 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *091302* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary Amendment

1) Acknowledgment is made of Applicants' preliminary amendment filed 07/11/02. With this, Applicants have amended the specification.

Election

2) Acknowledgment is made of Applicants' election filed 10/09/03 in response to the restriction requirement mailed 09/08/03. Applicants have elected, with traverse, of invention I, claim 14. Applicants contend that claim 1 of Arumugham *et al.* (EP 0941738, already of record) specifies an antigenic conjugate wherein a carrier protein is covalently bonded to the conserved portion of a gram negative bacterial lipopolysaccharide which comprises the lipid A portion in addition to the inner core. Applicants submit that their invention is more restricted, requires the lipopolysaccharide core of the *Neisseria* spp., and does not require conjugation. Therefore, Applicants conclude that Arumugham *et al.* is not novelty-destroying.

Applicants' arguments have been carefully considered, but are non-persuasive. With the use of the open claim language 'comprising' instant claim 1, for example, does not exclude, but includes any element other than inner core, including the lipid A portion. It is noted that lipid A is a part of the structure recited in the instant claim 13. Furthermore, claim 26, which depends from claim 1, is in fact drawn to a conjugated vaccine, and therefore, the instant invention is inclusive of a conjugated vaccine. In other words, a conjugated vaccine is not excluded from the scope of claim 1. Clearly, the special technical feature does not define over the disclosure of Arumugham *et al.* The lack of unity held in the instant application is proper and is hereby made FINAL.

Claim 20 was inadvertently left out of the lack of unity grouping and is hereby joined with the elected invention.

Status of Claims

3) Claims 4, 5, 9-14, 17, 19-22, 24-27, 35-37 and 41 have been amended via the amendment filed 07/11/02.

Claims 1-41 are pending.

Claims 19 and 29-41 have been withdrawn from consideration as being directed to non-elected inventions. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

The elected claim 14, and the linking claims 1-13, 15-18 and 20-28 are under examination. An Action on the Merits for these claims is issued.

Priority

4) The instant application is a national stage 371 application of PCT/GB00/03758 filed 10/02/00, now abandoned, which claims priority to the U.S. provisional applications, 60/196,305 filed 04/12/00 and 60/156,940 filed 09/30/99.

Specification - Informalities

5) The instant specification is objected to because:

(i) The first paragraph of the specification does not provide information on the prior application(s) as indicated above under 'Priority'.

(ii) The specification on page 18 lacks the title 'Brief Description of the Drawings'. See 37 C.F.R 1.74. The subheading 'Statement of invention' should be replaced with Summary of Invention--. See 37 C.F.R 1.73.

(iii) Figures 1 and 15 are incorrectly numbered. The different panels in the Figures should be individually renumbered. For example, the drawings for Figures 1 and 15 have two panels, which should be labeled as Figures 1A and 1B and Figures 15A and 15B respectively. Figure 3 has three panels labeled as a, b and c; Figure 5 has four panels a, b, c and d; Figure 6 has two panels a and b; and Figure 7 has five panels a-e. However, the description of these Figures on pages 18-20 do not refer to these Figures as 'Figures 1A and 1B'; 'Figures 15A and 15B'; 'Figures 3a-3b' and so on. Individual Figure descriptions on pages 18-20 in the specification should be amended accordingly. All references to these Figures in the specification should be amended to reflect these changes in numbering.

(iv) Figure 1 does not include a region wherein a part of the depicted structure is indicated in 'bold' letters as alleged in the first full paragraph on page 46 of the specification.

(v) The use of the trademarks in the instant specification has been noted in this application. For example, see page 27: "Nunc maxisorp" and 'Tween 20'; page 28, first full paragraph: 'Nunc Maxisorp'; page 53, first full paragraph: 'Trypan Blue'; and page 54, second full paragraph: 'sepharose'. Although the use of trademarks is permissible in patent applications, the propriety nature of the trademarks should be respected and every effort made to prevent their use in

any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification and make necessary changes wherever trademark recitations appear.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

6) Claims 14 and 16 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological material is (1) known and readily available to the public; (2) reproducible from the written description, e.g. sequenced; or (3) deposited.

Claims 14 and 16 are directed to a vaccine comprising an immunogenic component that is reactive with the B5 antibody produced by the specific hybridoma. It is apparent that this monoclonal antibody is required to practice the claimed invention. As a required element, the monoclonal antibody or hybridoma must be known and be readily available to the public, or obtainable by a reproducible method set forth in the specification, or otherwise be readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the hybridoma producing the monoclonal antibody.

From the fourth full paragraph on page 6 of the instant specification, it appears that the recited hybridoma cell line has been deposited at an international depository authority (IDA). However, the exact name of the depository and the full address are currently lacking in the specification to make a determination as to whether the this is a recognized IDA and whether or not Applicants are in compliance with 37 C.F.R § 1.801-1.809. If the deposits have already been made under the provisions of the Budapest Treaty, filing of a signed affidavit or declaration by Applicant or assignees, or a statement by an attorney of record having a registration number who has authority and control over the conditions of deposit stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that **all** restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application, is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each state. Further, the statement should identify the deposited hybridoma by its depository accession number, establish that the deposited hybridoma cell line is the same as the one described in the specification

and that the deposited hybridoma cell line was in Applicant's possession at the time of filing. As a means of satisfying the necessary criteria of the deposit rules and to show that the deposited hybridoma cell line producing the recited monoclonal antibody is the same as the one deposited, Applicants may submit a copy of the contract or a notice of acceptance of the hybridoma cell line by the depository.

Applicant's attention is directed to *In re Lundack*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 C.F.R § 1.801-1.809 for further information concerning deposit practice.

7) Claims 1-18 and 20-28 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an immunogenic composition comprising a formalin-killed whole cell vaccine of a *galE* mutant of *Neisseria meningitidis* which on active immunization elicits antibodies reactive with the LPS inner core of said *galE* mutant and a neisserial inner core LPS epitope containing phosphatidylethanolamine at position 3 of HepII, and antibodies bactericidal against the homologous *galE* mutant of *Neisseria meningitidis*, does not reasonably provide enablement for a vaccine therapeutically or prophylactically functional or effective in curing or preventing any systemic or local meningococcal infections, including septicaemia, pneumonia, meningitis, or gonococcal infections including sexually transmitted diseases, such as, urethritis, cervicitis, proctitis, pharyngitis, salpingitis, epididymitis and bacteremia/arthritis, as claimed broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant application, the vaccine, as claimed, is required to induce 'functional antibodies'

against 'a majority of the strains within the species of the pathogenic *Neisseria'*, or against at least 60%, 70%, 85% or 95% of the strains within the species of the pathogenic *Neisseria*. The limitation 'a majority of the strains within the species of the pathogenic *Neisseria*' is so broad that it encompasses an infinite number of strains of pathogenic *Neisseria* species, including those yet to be discovered, and those whose pathogenetic nature or mechanism is yet to be established. Claim 22 is directed to a 'vaccine' 'for the treatment of *Neisseria meningitidis*'. The species of the pathogenic *Neisseria* encompassed in the limitation are not identified and the nature of their pathogenesis is not described. Without the disclosure of the precise pathogenesis caused by a representative number of these unknown strains of unspecified species of pathogenic *Neisseria* and without the establishment, via an art-accepted *in vivo* animal model, or an *in vitro* assay that is correlative of protection, that the claimed 'vaccine' elicits 'functional' or protective antibodies against all these unspecified strains and unspecified species of pathogenic *Neisseria*, one of skill in the art would not be able to practice the invention as claimed without considerable amount of undue experimentation. Claim 24 is directed to a vaccine comprising an immunogenic component based on the inner core of a *Neisseria* lipopolysaccharide for the 'prevention' of meningitis, septicaemia, pneumonia or other manifestation of systemic or local disease occasioned by *Neisseria meningitidis*. However, the disclosure is not enabling for a method of "preventing" such diseases in any subject, including a human. The *Webster's II New Riverside University Dictionary* (1984) defines the term "prevent" as "to keep from happening". Infection due to *Neisseria meningitidis* encompasses microbial cell invasion and growth or multiplication of the bacteria. The term "infect" is defined in the illustrated *Stedman's Medical Dictionary* (24th Edition, 1982) as "to enter, invade, inhabit, or to dwell internally". The specification is not supportive of a vaccine which keeps the process of meningitis, septicaemia, pneumonia or other manifestations of systemic or local disease occasioned by *Neisseria meningitidis* from happening, or a vaccine which prevents the entry/invasion of *Neisseria meningitidis* into a cell or its internal dwelling on administration of the vaccine of the instant invention to a subject or patient. There is absolutely no evidence within the instant specification to show that the vaccine as claimed did in fact 'prevented' the invasive process, or meningitis, septicaemia, pneumonia or other manifestation of systemic or local disease occasioned by *Neisseria meningitidis* from happening. The ability to reproducibly practice the claimed invention is well outside the realm of routine

experimentation.

The specification in the third full paragraph on page 13 mentions that meningococcal diseases that are to be treated or prevented by the vaccine include meningitis, septicaemia and pneumonia, and the gonococcal diseases that are to be treated or prevented by the vaccine include sexually transmitted diseases, such as, urethritis, cervicitis, proctitis, pharyngitis, salpingitis, epididymitis and bacteremia/arthritis. This part of the specification further makes a broad statement that the invention extends to treatment and prevention of any other disease which results from *Neisseria* infection. The specification describes a method of evaluating the cross-reactivity and the binding functions of a monoclonal antibody, B5. The B5 monoclonal antibody is **not** elicited by a vaccine comprising the isolated LPS inner core immunogenic component, with or without conjugation to an isolated T cell-dependent biomolecule, but is produced by immunizing mice with formalin-killed whole cells of a *galE* mutant of *N. meningitidis* H44/76 (B.15.P.1.7.16 immunotype L3). See first full paragraph on page 21. This part of the specification describes the reactivity of the B5 monoclonal antibody with the core LPS of group A, B, C, W, X, Y and Z strains of *N. meningitidis*. The of the specification further speculates the 'possibility' that immunogens capable of eliciting functional antibodies specific to inner core structures 'could be' the basis of a vaccine against invasive infections caused by *N. meningitidis*. The specification acknowledges that, in summary, what is being described in the instant application is the reactivity of the B5 monoclonal antibody with a cross-reactive epitope on the LPS of the majority of naturally occurring, but genetically diverse strains of *N. meningitidis*. The specification describes the specific epitope recognized by the B5 monoclonal antibody. The *galE* LPS-specific monoclonal antibodies were produced by immunizing mice with three intraperitoneal injections followed by one intravenous injection with 'formalin-killed *galE* mutant whole cells'. The resultant monoclonal antibodies were used for screening or immunotyping *N. meningitidis* using a whole cell or LPS ELISA, immunoflourescence or HUVEC assay. See pages 26-28. The 'Results' section of the specification describes the cross-reactivity of the IgG3 monoclonal antibody, B5, with various neisserial or non-neisserial LPSs and appears to identify the specific epitope of the B5 monoclonal antibody to be PEtn attached at the 3-position of HepII. A mere showing that a monoclonal antibody elicited by whole cells of *galE* mutant of *N. meningitidis* reacts with different capsular and non-capsular strains of *N. meningitidis* and some strains of *N. gonorrhoeae* via an *in*

vitro or *in vivo* binding assay does not constitute adequate enabling disclosure for a vaccine that is therapeutic or prophylactic against any systemic or local meningococcal infections, including septicaemia, pneumonia, meningitis, or any gonococcal infections including sexually transmitted diseases, such as, urethritis, cervicitis, proctitis, pharyngitis, salpingitis, epididymitis and bacteremia/arthritis. The following statement on page 35 of the specification provides the evidence that the claimed product as a 'vaccine' for the treatment or prevention of the above-cited diseases is not enabled:

> Future studies will look at the safety and immunogenicity of inner core LPS-conjugates (PEtn at 3-position of HepII and alternative glycoforms) and the functional ability of these polyclonal antibodies in opsonic and serum bacterial assays, initially in mice and rabbits.

The specification on page 35 states as follows:

> Preliminary studies using MAb B5 in an opsonophagocytosis assays with *Neisseria meningitidis* strain MC58 and donor human polymorphonuclear cells suggest MAb B5 is opsonic in the presence of complement and that the uptake of *Neisseria meningitidis* bacteria correlates with an oxidative burst reaction within the neutrophil. Mab B5 does not appear to have any significant serum bactericidal activity with *Neisseria meningitidis* strain MC58, however this is not unexpected in view of its isotype (IgG3). The functionality of MAb B5 is currently under further investigation.

An enabling disclosure or convincing evidence is critical in light of the unpredictability involved in eliciting functional antibodies by an antigens of a pathogenic bacterium, including the antigens of pathogenic *Neisseria*. The art reflects unpredictability with regard to the protective and bactericidal nature of antibodies induced by bacterial polysaccharides, including the *Neisserial* LPS. For example, Tarkka *et al.*(*Microb. Pathogen.* 6 (5): 327-335, May 1989) taught the following (see page 332):

> Antibodies to cell surface components, including the capsular polysaccharide, LPS and class 1 OMP have been shown protective in this model, whereas antibodies to the class 2/3 porins (although bactericidal) were, as a rule, not protective.[6] We have also tested antibodies to another MenB OMP, the H.8 antigen[24] in this model, and seen no protection (unpublished data). The anti-28 kDa mouse serum HH7 was also completely without effect on the MenB infection. This finding is in accordance with the bactericidal assay result, and adds support to the use of the bactericidal assay as a predictor of protection. It is also in accordance with increasing evidence suggesting that only few OM components of meningococci can serve as targets for protective antibodies.[17,25] ..... Possible vaccine components may be few.

Thus, antibodies that are shown to be bactericidal *in vitro* are not necessarily protective *in vivo*. The art reflects that while some monoclonal antibodies elicited by the neisserial LPS were protective against homologous immunotype or against the same bacteria, other monoclonals were not. For

example, an anti-LPS monoclonal antibody despite having a bactericidal titer as high as 1280 showed 100% mortality rate in an *in vivo* animal model. See page 6 and Table 1 of Saukkonen *et al.* (*Publications of the National Public Health Institute*, Helsinki, A1/1988, pages 1-13, 1988). It has been reported that anti-neisserial LPS IgG3 antibodies to fix complement very poorly. The art also taught that meningococcal LPS differs due to growth conditions suggesting structural variability based on the environment meningococci are in. Furthermore, those of skill in the art have expressed caution and suggested that care should be taken when correlating bactericidal (functional) activity with protective efficacy. See page 7 of Saukkonen *et al.*

In the instant application, the specification states that MAb B5 has been shown to have opsonic and bactericidal activity against the homologous *galE* mutant and an ability to passively protect infant rats against challenge with the 'homologous *N. meningitidis galE* mutant'. See last full paragraph on page 52 and section iii) on pages 57 and 58 of the specification. Section ii) on page 56 of the specification states that B5 MAb had opsonic activity against *N. meningitidis* MC58 and BZ157 strains and against the *galE* mutant strain. Section ii) on page 57 of the specification states that B5 MAb had bactericidal activity against the homologous *N. meningitidis galE* mutant strain. This however does not establish that the claimed vaccine, when administered *in vivo* by active immunization to a mammal, including a human, would induce antibodies that would be curative, or that would prevent any infections caused by a majority of meningococcal strains, including septicaemia, pneumonia and meningitis caused by non-galE mutant strains of *N. meningitidis*, or any gonococcal infections including sexually transmitted diseases, such as, urethritis, cervicitis, proctitis, pharyngitis, salpingitis, epididymitis and bacteremia/arthritis caused any strain of *N. gonorrhoeae*. There is absolutely no evidence within the instant specification to show that the B5 MAb had any protective activity, *in vivo* or *in vitro*, against any strains of *N. gonorrhoeae*, which are well known in that art to undergo frequent antigenic variation. A mere binding of an anti-LOS antibody to the homologous *N. meningitidis galE* mutant strain, or to a few non-galE mutant strains of *N. meningitidis*, and a showing of *in vitro* bactericidal activity with the homologous *N. meningitidis galE* mutant strain, or a passive protection against the homologous *N. meningitidis galE* mutant strain are insufficient to enable a vaccine as claimed that is prophylactic or therapeutic against a wide variety of systemic and local diseases caused by a majority of virulent and invasive, wild type,

antigenically and genetically diverse, non-galE mutant strains of *N. meningitidis*, or any virulent strain of *N. gonorrhoeae*, or any other pathogenic *Neisseriae*, as claimed broadly. There is neither a disclosure, nor is it predictable that if one administered the claimed vaccine composition to a host, such as a human, it would be prophylactically or therapeutically effective or functional against any or all of the above-cited clinical conditions of meningococcal or gonococcal origin, as claimed. The protective, therapeutic or prophylactic efficacy of a bacterial antigen or vaccine is not a predictable event, but requires a concrete showing of a beneficial effect in an acceptable *in vivo* animal model, or via *in vitro* experiments that are recognized in the art to correlate with the protective, therapeutic or prophylactic efficacy using a representative number of 'a majority of the strains within the species of the pathogenic *Neisseria*' as challenging strains. The instant specification lacks evidence showing that the claimed vaccine is protective against 60-95% of strains of a given pathogenic *Neisseria* species. The instant specification lacks enabling disclosure in this regard

Due to the lack of specific disclosure and/or guidance, the lack of working examples enabling a preventive product, the breadth of the instant claims, the art-recognized unpredictability factor, and the quantity of experimentation necessary, undue experimentation would have been required at the time of the effective filing date of the instant application for one of ordinary skill in the art to reproducibly make and use the claimed vaccine. The scope of enablement provisions of 35 U.S.C. § 112, first paragraph, are not met.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

8) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

9) Claims 1-18 and 20-28 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague and indefinite in the recitation: 'comprising, an immunogenic component based on the inner core ..', because it is unclear what do Applicants mean by 'based on the inner core'. What immunogenic or non-immunogenic elements are encompassed in this limitation is not clear.

(b) Analogous criticism applies to claim 15.

(c) Claims 1-3, 15, 17 and 18 are vague and indefinite in the limitation 'functional antibodies', because it is unclear what properties an antibody should have in order to qualify as a 'functional' antibody. For instance, does an antibody showing specific or non-specific binding qualify as a 'functional' antibody. Do non-opsonic and/or non-bactericidal qualify as functional antibodies?

(d) Claims 15 and 17 are vague in the recitation 'few immunogenic components based on the inner core', because it is unclear how many immunogenic components are encompassed in this limitation. It is further unclear what constitute the 'few immunogenic components based on the inner core'. Do these components include phosphoethanolamine immunogenic component, GlcNAc component, Kdo components etc.?

(e) Claim 4 is vague and indefinite in the recitation: 'substantially free from outer core', because it is unclear how much of the outer core lipopolysaccharide's original structure has to be retained such that the resulting product can be considered 'substantially free from outer core' is not clear.

(f) Claims 6-8, 17 and 18 are vague, indefinite and confusing in the recitation: antibodies are elicited by the immunogenic component 'in' at least ...% of .... strains ... of *Neisseria* ...., because it is unclear how antibodies are produced by the immunogenic component(s) of the claimed vaccine 'in', i.e., inside pathogenic *Neisseria* or group B strains of *Neisseria meningitidis*.

(g) Claims 9 and 10 are vague and indefinite in the recitation 'functional equivalent thereof' because it is unclear what is encompassed in this limitation. It is not clear what structural or non-structural characteristics a component should have in order to qualify as a "functional equivalent thereof' as recited. How much of the *Neisseria* LPS's original structure has to be retained such that the resulting product can be considered as a 'functional equivalent thereof', is not clear. The metes and bounds of the structure encompassed in the limitation 'functional equivalent' is indeterminate.

(h) Claim 9 is vague and indefinite in the recitation: "derived from this inner core ", because it is unclear what is encompassed in the process of 'deriving'. Does the process of "deriving" encompass: extraction, isolation, separation, purification, modification or expression?

(i) Claim 27 is vague and indefinite in the recitation: "derived from ", because it is unclear what is encompassed in the process of 'deriving'. Does the process of "deriving"

encompass: extraction, isolation, separation, purification, modification or expression?

(j) Claim 14 is vague and indefinite fro failing to distinctly claim the subject matter in the recitation 'B5 antibody produced by the hybridoma' without particularly identifying the B5 antibody as a --monoclonal-- antibody.

(k) Claim 9 appears to lack proper antecedence in the limitation 'a *Neisseria* LPS'. Claim 9 depends from claim 1, which already includes the limitation 'a *Neisseria* .... LPS'. It is unclear whether this *Neisseria* LPS is the same as the one recited in claim 1, or whether this is in addition to the one recited in claim 1. If the former is true, for proper antecedence, it is suggested that Applicants replace the limitation with 'the *Neisseria* LPS'.

(l) Claims 2, 3, 17 and 18 are redundant in the antecedence 'the said' (see line 1). To be consistent with the claim language used in claims 6-12 for example, it is suggested that Applicants delete the recitation 'said'.

(m) Claims 2-18 and 21-28 lack proper antecedence in the limitation: 'A vaccine according to claim ....'. For proper antecedence, it is suggested that Applicants replace the limitation with --The vaccine according to claim .....--.

(n) Claim 21 is indefinite and confusing in the limitation: "vaccine according to claim 1, comprising one or more immunogen components which are capable of stimulating antibodies which are opsonic', because it is unclear how the 'immunogen components' of claim 21 differ from the 'immunogenic component' of claim 1 from which claim 21 depends.

(o) Claim 21 is further confusing in the limitation: 'antibodies which are opsonic', because it is unclear what structure, bacterium or pathogen the antibodies are opsonic against.

(p) Claims 22 and 23 are vague, indefinite and/or confusing in the limitation: 'for the treatment of *Neisseria meningitidis* ....', because it is unclear how a vaccine can treat a bacterium as opposed to a disease or a clinical condition caused by a pathogenic bacterium. Is this treatment equivalent to *in vitro* treatment in a test tube for example?

(q) Claims 24 and 25 are vague, indefinite and/or confusing in the limitation: 'other manifestation of systemic or local disease occasioned by ..', because it is unclear what manifestations are encompassed in this limitation.

(r) Claim 20 has improper antecedence in the recitation: 'the bacterium'. Claim 20

depends from claim 1, which does recite a 'bacterium'.

(s) Claim 9 is vague and indefinite in the recitation: 'a part ... of the inner core structure'. How much of the inner core's original structure has to be retained such that the resulting product can be considered as a 'a part .... of the inner core structure', is not clear. The metes and bounds of the structure encompassed in the limitation is indeterminate.

(t) Claims 1 and 15 are vague and indefinite in the recitation: 'a majority of the strains within the species of the pathogenic *Neisseria*', because it is unclear what quantity is encompassed in the limitation. Does this limitation represent majority of the strains tested in a given experiment, or majority of the strains prevalent in a given locality? Does the limitation encompass yet to be discovered species within the species of the pathogenic *Neisseria*?

(u) By the recitation 'B5 antibody', claim 14 fails to distinctly claim the subject matter. B5 is describes in the specification as a 'monoclonal' antibody. It is suggested that Applicants replace the recitation with --B5 monoclonal antibody--.

(v) Claim 24 is indefinite in the recitation: 'vaccine according to claim 1 for the prevention of'. Claim 24 depends from claim 1 which is drawn to a vaccine 'for the treatment of'. It is unclear whether the vaccine claimed in claim 24 is for 'treatment' or for 'prevention'.

(w) Claims 2-3, 6-8, 17 and 18 are vague, indefinite and confusing in the recitation: '% of the strains within the species of the pathogenic *Neisseria*' because it is unclear which species of pathogenic *Neisseria* are included, and whether the percentatge is calculated based on the number of strains within the species tested in a given experiment, or the number of prevalent strains within the species.

(x) Claims 2-18 and 20-28, which depend directly or indirectly from claim 1 or claim 21, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

10) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11) Claims 1-12, 14-18 and 20-26 are rejected under 35 U.S.C § 102(b) as being anticipated by Arumugham *et al.* (EP 0941738) as evidenced by Carbonetti *et al.* (US 5,736,361).

The transitional limitation "comprises" similar to the limitations such as, "has", "includes," "contains," or "characterized by," represents open-ended claim language and therefore does not exclude additional, unrecited elements, for example, lipid A moiety. See M.P.E.P 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). On the other hand, the limitation "consisting of" represents closed claim language and excludes any element, step, or ingredient not specified in the claim. *In re Gray, 53 F.2d 520, 11 USPQ 255 (CCPA 1931)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)*.

Arumugham *et al.* disclosed a vaccine comprising a conserved inner core portion of a Gram negative bacterial, such as, meningococcal or gonococcal lipopolysaccharide (LPS) capable of eliciting antibodies that are cross-functional and cross-reactive with heterologous strains of said Gram negative bacteria. The vaccine is for preventing diseases caused by a large number of heterologous strains of Gram negative bacterial pathogens and against heterologous strains within a given genus and heterologous bacterial genera. See abstract; sections [0013], [0016], [0017] and [0018]. The vaccine is for the prophylaxis of septic shock and endotoxin-induced complications caused by *Neisseria*, i.e., other manifestations of systemic or local disease occasioned by *Neisseria meningitidis* or *Neisseria gonorrheoae*. The conserved inner core portion includes the glucosamine disaccharide substituted with phosphates, phosphoethanolamine groups, the KDO function of the inner core and the heptose substituents. The phosphoethanolamine groups may also be contained in the conserved inner core portion. See section [0019]. The vaccine is a conjugated vaccine. The LPS portion present in the vaccine contains only the conserved core LPS structure of *Neisseria meningitidis* having the structure identified by GlcNAc-Hep_2phosphoethanolamine-KDO_2. See section [0046]. The structure of the LPS core of *Neisseria gonorrhoeae* is depicted in Figure 3B, which has a glucose residue at HepI and an N-acetyl glucosamine at HepII, and is the same as the one recited in instant claims, or a functional equivalent of the same. The conserved portion of the

LPS in the vaccine is conjugated with a carrier protein, such as, outer membrane protein complexes of *Neisseria meningitidis* that contains class 1 outer membrane protein; outer membrane proteins of *Neisseria gonorrhoeae*. See section [0037] and therefore contains one or more immunogen components which are capable of stimulating opsonic antibodies. The vaccine induces T cell-dependent IgG response in the individual being treated and the antibodies induced are bactericidal, i.e., functional or immunoprotective and react with heterologous strains within a particular genus and heterologous genera. See section [0021]. The vaccine may contain whole or part of the conserved portion. See section [0022]. The vaccine contains a physiologically acceptable carrier or an adjuvant. See sections [0038] and [0040]. The vaccine is immunogenic when administered to mice and elicited antibodies that were reactive with the purified LPS or the whole cells (i.e., cells containing bacterial capsule) of majority of the strains of *Neisseria meningitidis* including R6, AI, H44/76, 2996, L1, L2, L3, L4, L5, L6, L7, L8, L10 and L11 strains (i.e., at least 50% to 85% of the strains within the same species of pathogenic *Neisseria*). See sections [0053] to [0055] and [0058]; and Table 2. The vaccine-induces antibodies reacted with the purified LPS of *Neisseria gonorrhoeae*. See sections [0059] and [0060]; and Figure 4. The antibodies elicited by the vaccine are functional, i.e., bactericidal against H44/76, 2996, A1 and R6 strains of *Neisseria meningitidis* and killed *Neisseria meningitidis* expressing different LPS immunotypes. See sections [0061] and [0062]; and Table 3. Although Arumugham *et al.* are silent about the reactivity of the prior art immunogenic component to the specific antibody recited in claim 14, the prior art immunogenic component is viewed as the same as Applicants' immunogenic component. Since the prior art immunogenic component is viewed as structurally the same as the one recited in the instant claim(s), it is expected to be reactive with Applicants' specific antibody, B5, which was inaccessible to Arumugham *et al.* at that time. The property of reactivity with the specific antibody, B5, recited by Applicants is an inherent property inseparable from the immunogenic component of Arumugham *et al.*

That the additional immunogen(s), such as, outer membrane protein complexes of *Neisseria meningitidis* containing class 1 outer membrane protein; or outer membrane proteins of *Neisseria gonorrhoeae* present in the prior art vaccine are capable of stimulating opsonic antibodies in inherent from the teachings of Arumugham *et al.* in light of what was well known in the art. For instance,

Carbonetti *et al.* taught the art-known fact that gonococcal outer membrane proteins stimulate opsonic antibodies which bind to the surface of the infecting pathogen (see lines 10-15 in column 5).

Claims 1-18 and 20-26 are anticipated by Arumugham *et al.* Carbonetti *et al.* is **not** used as a secondary reference in combination with Arumugham *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Arumugham *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

12) Claims 1, 27 and 28 are rejected under 35 U.S.C § 102(b) as being anticipated by Kim *et al.* (*Infect. Immun.* 56: 2631-2638, 1988).

Claims 27 and 28 are drawn to a vaccine which is derived from a commensal *Neisseria*, such as, *Neisseria lactamica*. The term 'vaccine' represents the intended use of the claimed product and therefore is not given any patentable weight. Since the claimed 'vaccine' is not required to be isolated and/or purified, a whole cell preparation of *Neisseria lactamica* reads on the instant claims.

Kim *et al.* taught whole-cell lysates and a lipooligosaccharide (LOS) extracted from the cells of *Neisseria lactamica*. Kim's *Neisseria lactamica* preparations contain conserved LOS epitopes of *Neisseria meningitidis* and *Neisseria gonorrhoeae* and are reactive with the monoclonal antibody, O6B4, which antibody also recognized the same cross-reactive epitopes in the LOS of serogroup A, B, C and Y; and L2,4; L3,7; L9; and L11 strains; and non-typeable strains of *Neisseria meningitidis*; as well as *Neisseria gonorrhoeae*. Kim's preparations are viewed as vaccines comprising an immunogenic component based on the inner core of *Neisseria lactamica* LPS. See 'Materials and Methods'; Tables 1-4; paragraph bridging left and right columns on page 2633, 2635 and 2637; and last full paragraph in left column on page 2637. The capability to elicit functional antibodies as recited in the instant claims is viewed as an inherent property inseparable from the prior art product.

Claims 1, 27 and 28 are anticipated by Kim *et al.*

13) Claims 1-18 and 20-25 are rejected under 35 U.S.C § 102(b) as being anticipated by Plested *et al.* (*Infect. Immun.* 67: 5417-5426, October 1999 - Applicants' IDS).

Instant claims are not granted priority to 09/30/99 since the specification of the provisional applications 60/156,940 and 60/196,305 lack enabling disclosure for a 'vaccine' that elicits functional antibodies and that prevents or treats the variously recited diseases.

It is noted that the Plested reference is authored by Plested, Makepeace, Jennings, Gidney,

Lacelle, Brisson, Cox, Martin, Bird, Tang, Mackinnon, Richards and Moxon, and therefore qualifies as prior art by 'another' under 35 U.S.C § 102(a).

The term 'vaccine' is viewed as representing the intended use of the product and therefore is not given any patentable weight. The preamble limitations: 'for the prevention of meningitis ..... disease occasioned by *Neisseria meningitidis*' in claim 24; 'for the treatment of *Neisseria meningitidis*' in claim 22; and 'for the treatment of urethritis, salpingitis, cervicitis, proctitis, pharyngitis, pelvic inflammatory disease or other manifestation of systemic or local disease occasioned by *Neisseria gonorrhoeae*' represent the intended use of the claimed product.

Plested *et al.* taught an immunogenic composition comprising a formalin-killed *galE* mutant whole cells of group B *N. meningitidis*, which elicited the B5 mAb antibody specific to LPS inner core (see page 5419, right column). Plested *et al.* taught an immunogenic composition comprising conserved and accessible inner core lipopolysaccharide of *N. meningitidis* which is recognized by the B5 monoclonal antibody. The B5 mAb recognized 76% of strains of group B *N. meningitidis* and also reacted with the inner core LPS of wild-type encapsulated *N. meningitidis* (see abstract). The meningococcal inner core LPS consists of an inner core oligosaccharide attached to lipid A and has the general formula identical to the one recited in the instant claim 13. The inner core LPS contains an epitope recognized by the monoclonal antibody, B5, and is characterized by the presence of a phosphoethanolamine moiety linked to the 3-position at HepII of the inner core, a glucose residue at HepI, an N-acetyl glucosamine at HepII of the inner core LPS (see the upper panel of Figure 1 including the right most area indicated in bold letters). The B5 monoclonal antibody specifically reacted with the majority of the *N. meningitidis* strains tested by dot blot, i.e., 10 out of 12 strains (see Table 2) and also with *N. lactamica* strains (see page 5423, right column). The mAb B5 induced by the inner core-based formalin killed meningococcal galE mutant whole cell vaccine is opsonic (see page 5425). That the prior art formalin killed meningococcal galE mutant whole cell vaccine comprises one or more immunogenic components other than the inner core-containing LPS is inherent from the teachings of Plested *et al.* since whole cell vaccines are known to contain multiple antigens in addition to the LPS. Since the structure of the prior art inner core LPS is identical to the structure of the inner core LPS of the instant invention, the prior art product is expected to elicit functional antibodies to at least 85% or 95% of the strains within *N. meningitidis*.

Claims 1-18 and 20-25 are anticipated by Plested *et al.*

14) Claims 1-12, 14-18, 20-22 and 26 are rejected under 35 U.S.C § 102(b) as being anticipated by Verheul *et al.* (*Infect. Immun.* 59: 843-851, 1991) as evidenced by Plested *et al.* (*Infect. Immun.* 67: 5417-5426, October 1999 - Applicants' IDS).

The recitation 'a majority of the strains' in claims 1 and 15 is viewed as a relative term.

Verheul *et al.* taught meningococcal L2 and meningococcal L3, L7,9 phosphoethanolamine-containing oligosaccharide-protein conjugates that are immunogenic in rabbits, with or without the use of Quil A adjuvant, and that elicit high levels of IgG antibodies specific to PEA-containing epitopes. Rabbits were also immunized with the unconjugated LPS (see page 845, left column, first full paragraph). LPS alone and LPS conjugates elicited specific IgG responses (see Figure 3 and page 848). Verheul *et al.* also taught whole cell meningococcal bacteria which elicit antibodies directed against PEA-containing epitopes (see abstract; and page 850, left column). The structure of the meningococcal LOS is depicted in Figure 1 which shows the presence of heptoses, kDO, GluNAc, glucose and PEA. By ELISA and inhibition ELISA, the conjugate-induced antibodies were shown to be reactive with PEA-containing whole meningococcal organisms (and therefore with accessible epitopes), LOS and OS (see page 850). That the antibodies elicited by the prior art vaccine are specific to PEtn in the 3-position of HepII and are opsonophagocytically functional is inherent from the teachings of Verheul *et al.* in light of what is known in the art. For instance, Plested *et al.* taught that some antibodies elicited by Verheul's oligosaccharide conjugate vaccine comprising PEtn in the 3-position of HepII has immunogenic and opsonophagocytic activity (see paragraph bridging pages 5424 and 5425). Since the prior art inner core LPS contains the phosphoethanolamine-containing epitope similar to the one recited, the prior art product is expected to elicit functional antibodies to at least 60% to 95% of the strains within *N. meningitidis*.

Claims 1-12, 14-18, 20-22 and 26 are anticipated by Verheul *et al.* Plested *et al.* is **not** used as a secondary reference in combination with Verheul *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Verheul *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

Objection(s)

15) Claims 1, 9, 13 and 16 are objected to for the following reasons:

(a) Claim 1 lacks a preceding article in between the recitation 'of disease'. It is suggested that Applicants replace the limitation with --of a disease--.

(b) In line 3 of claim 9, for clarity, it is suggested that Applicants replace the limitation 'this inner core' with --the inner core--.

(c) In line 2 of claim 13, for clarity, it is suggested that Applicants delete the recitation 'as shown'.

(d) Claims 16 is objected to under 37 C.F.R 1.75(c) as being in improper form because a multiple dependent claim must refer to other claims from which it depends in the alternative only. In this case, each of these claims depends from previous claims in the cumulative form. See MPEP 608.01(n).

Remarks

16) Claims 1-18 and 20-28 stand rejected.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The TC 1600 facsimile center receives transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

18) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number until January 2004 is (703) 308-9347 and (571) 272-0854 beginning February 2004. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER